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Special Focus: Molecular and Cellular Events Controlling Neuronal and Brain Function and Dysfunction

Oxidative stress in Alzheimer disease

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Abbreviations: AGEs, advance glycation end products; AD, Alzheimer disease; Aβ, amyloid β peptide; APP, amyloid precursor protein; GSH, glutathione; HNE, 4-hydroxy-2,3-nonenal; 8OHdG, 8-hydroxy-2-deoxyguanosine; 8OHD, 8-hydroxyguanosine; MAP-tau, hyperphosphorylated microtubule-associated protein tau; NFTs, neurofibrillary tangles; NFκB, nuclear transcription factor κB; ROS, reactive oxygen species

Key words: ageing, advanced glycation endproducts, Alzheimer disease, amyloid, oxidative stress

Alzheimer disease (AD) is a progressive dementia affecting a large proportion of the aging population. The histopathological changes in AD include neuronal cell death, formation of amyloid plaques and neurofibrillary tangles. There is also evidence that brain tissue in patients with AD is exposed to oxidative stress (e.g., protein oxidation, lipid oxidation, DNA oxidation and glycoxidation) during the course of the disease. Advanced glycation endproducts (AGEs) are present in amyloid plaques in AD, and its extracellular accumulation may be caused by an accelerated oxidation of glycated proteins. AGEs participate in neuronal death causing direct (chemical) and indirect (cellular) free radical production and consequently increase oxidative stress. The development of drugs for the treatment of AD that breaks the vicious cycles of oxidative stress and neurodegeneration offer new opportunities. These approaches include AGE-inhibitors, antioxidants and anti-inflammatory substances, which prevent free radical production.

Introduction

Alzheimer disease (AD) is a progressive dementia afecting a large proportion of the aging population. A lot of attention has been focused on the histopathological changes in AD, including widespread neuronal cell death, the formation of amyloid plaques and neurofibrillary tangles (NFTs). The major component of the amyloid plaques is amyloid β-peptide (Aβ). Although Aβ is toxic to neurons in cell culture, Aβ deposits formed by overexpression of the amyloid precursor protein (APP) in transgenic mice does not cause suficient neuronal death, suggesting that additional factors are necessary to promote the progression of the disease. Early signs of tangle formation in certain brain regions such as the entorhinal cortex precede the clinical diagnosis of AD. The major component of NFTs is hyperphosphorylated microtubule-associated protein tau (MAP-tau). The abnormal MAP-tau is resistant to proteolitic enzymes suggesting that glycation, disulphide bond formation, phosphorylation and/or formation of core fragments contribute to extensive cross-linking between MAP-tau monomers.

We will introduce "advance glycation end products" (AGEs) and oxidative stress as the interacting key factors, promoting the transformation of soluble proteins into insoluble proteins deposits, as well as activating the microglia through specific ligands for cell surface receptors.

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Oxidative Stress and Alzheimer Disease

There is overwhelming evidence that brain tissue in AD patients is exposed to oxidative stress during the course of the disease (Fig. 1). Since oxidative stress is characterized by an imbalance in radical production of reactive oxygen species (ROS) and antioxidative defense, both are considered to have a major role in the process of age-related neurodegeneration and cognitive decline.[1-9]

Evidence of oxidative stress in AD is manifested through high levels of oxidised proteins, advanced glycation end products, lipid peroxidation end products, formation of toxic species, such as peroxides, alcohols, aldehydes, free carbonyles, ketones, cholestenone and oxidative modifications in nuclear and mitochondrial DNA.[10-21]

Age-related memory impairments correlate with a decrease in brain and plasma antioxidants defense mechanism.[22,23] An important aspect of the antioxidant defense system is the low molecular weight reducing equivalent glutathione, which is responsible for the endogenous redox potential in the cell.[24] The most important function of glutathione is to donate electrons to ROS and by doing so to scavenge them. Intracellular glutathione (GSH) concentration decreases with age in different animal models,[25-30] and it also decreases in aged mammalian brain regions including hippocampus.[31-33] The decrease in GSH leads to a situation where the rate of ROS production exceeds the antioxidant ability, generating a situation that favors oxidative stress. A further reason for oxidative stress is caused by an imbalance among the radical detoxifying enzymes in AD.[34]

Protein Oxidation

ROS mediated oxidation of protein side-chains has been reviewed,[35] and it results in the introduction of hydroxyl groups or in the generation of protein based carbonyls. Carbonyl groups are introduced in proteins by oxidizing amino acid residue side-chain hydroxyls into ketone or aldehyde derivatives.[36] A variety of oxidative pathways lead to carbonylation of proteins.[37] Carbonyl groups can also be introduced in proteins by direct oxidation of lysine, arginine, proline and threonine residues, or from the cleavage of peptide bonds by the α-amidation pathway or by the oxidation of glutamyl residues. ROS can also react with other molecules, such as lipids (lipid oxidation), DNA (DNA oxidation) and sugars (glycoxidation), resulting in the generation of reactive carbonyl derivatives and aldehydes, which may in turn react with proteins and form protein-bound carbonyls. Measurement of protein carbonylation is thought to be a good estimation for the extent of oxidative damage of proteins associated with various conditions of oxidative stress, aging, physiological disorders and AD.[38-40]

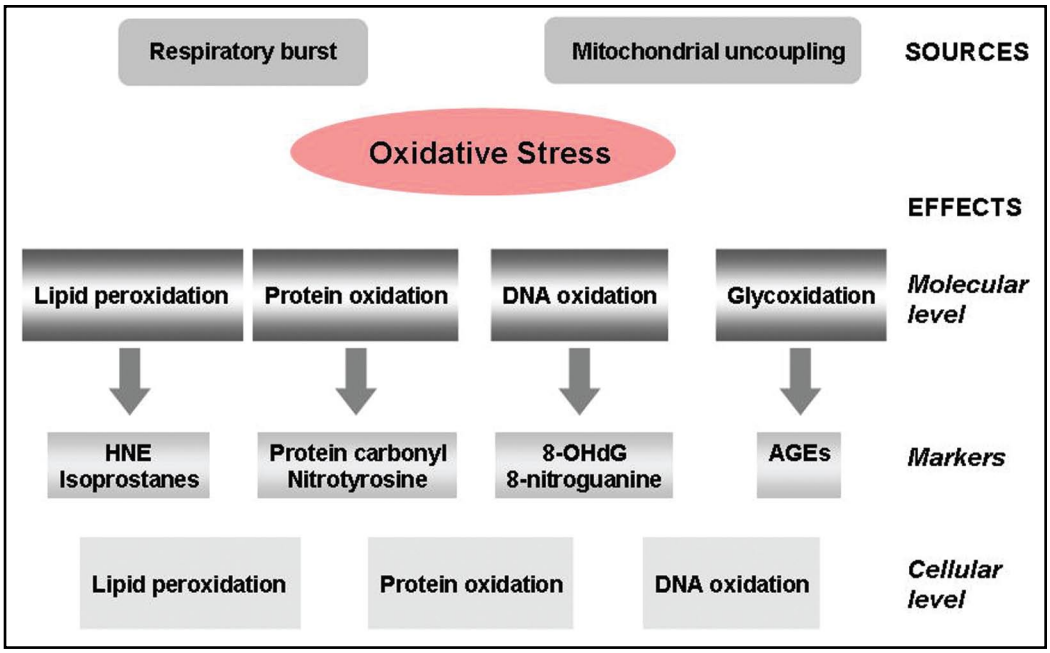

Figure 1. Sources and effects of oxidative stress on a molecular and cellular level.

Lipid Oxidation in AD

Aβ induces lipoperoxidation of membranes and lipid peroxidation products.[41] Lipids are modified by ROS and there is a strong correlation between lipid peroxides, antioxidant enzymes, amyloid plaques and NFTs in AD brains.[42] Several breakdown products of oxidative stress, including 4-hydroxy-2,3-nonenal (HNE), acrolein, malondialdehyde and F2-isoprostanes have been observed in AD brains compared to age-matched controls.[43-46] HNE is able to modify proteins, resulting in a multitude of effects, including inhibition of neuronal glucose and glutamate transporters, inhibition of Na-K ATPases, activation of kinases and dysregulation of intracellular calcium signalling, that ultimately induce an apoptotic cascade mechanism.[47-49] NFTs bear the footprints of oxidative membrane damage since they contain adducts of malondialdehyde and HNE, the most highly reactive lipid peroxidation products. Furthermore, dystrophic neurites of senile plaques that contain NFTs filaments show greater membrane damage than those that lack filaments. Evidence continues to mount that bifunctional HNE are the major cytotoxic products of lipid peroxidation. Following lipid peroxidation, a 2-pentylpyrrole modification of lysine is the only presently known "advanced" (stable end-product) adduct that forms from the modification of proteins by HNE in AD cases. These findings, together with the recent demonstration that HNE is cytotoxic to neurons and that it impairs the function of membrane proteins including the neuronal glucose transporter GLUT 3, indicate that HNE is a characteristic marker and a toxin leading to neurodegeneration in AD.[50]

DNA Oxidation in AD

DNA bases are vulnerable to oxidative stress damage involving hydroxylation, protein carbonylation and nitration.[21,51,52] It has been observed in AD that brain ROS induces calcium influx, via glutamate receptors and triggers an excitotoxic response leading to cell death.[48] ROS are generated when oxygen reacts with unregulated redox-active metals.[53] DNA and RNA oxidation is marked by increased levels of 8-hydroxy-2-deoxyguanosine (8OHdG) and 8-hydroxyguanosine (8OHD).[54-56] Furthermore, these markers have been localized in Aβ plaques and NFTs.[57] Increased levels of DNA strand breaks have been found in AD. They were first considered to be part of apoptosis, but it is now widely accepted that oxidative damage is responsible for DNA strand breaks and this is consistent with the increased free carbonyls in the nuclei of neurons and glia in AD. The induction of heme oxygenase-1, an antioxidant enzyme involved in the conversion of heme to bilirubin, is increased in AD brains and is tightly correlated with NFTs.

Glycoxidation in AD

Advanced glycation end products (AGEs), which are formed by a non-enzymatic reaction of sugars with long lived protein deposits, are also potent neurotoxins and proinflammatory molecules (Fig. 2). Glycation of proteins starts as a nonenzymatic process with the spontaneous condensation of ketone or aldehyde groups of sugars with a free aminoacid group of proteins to form a labile Schiff base, consistent with the classical reaction described by Maillard in 1912.[13] A cascade of reactions results thereafter in the formation of AGEs, which are composed of irreversibly cross-linked heterogeneous protein aggregates. There is increasing evidence that the insolubility of Aβ plaques is caused by extensive covalent protein cross-linking.[58] One mechanism by which long-lived proteins can be cross-linked involves AGEs.[59,60] Extracellular AGEs accumulation has been demostrated in senile plaques in different cortical areas in primi-

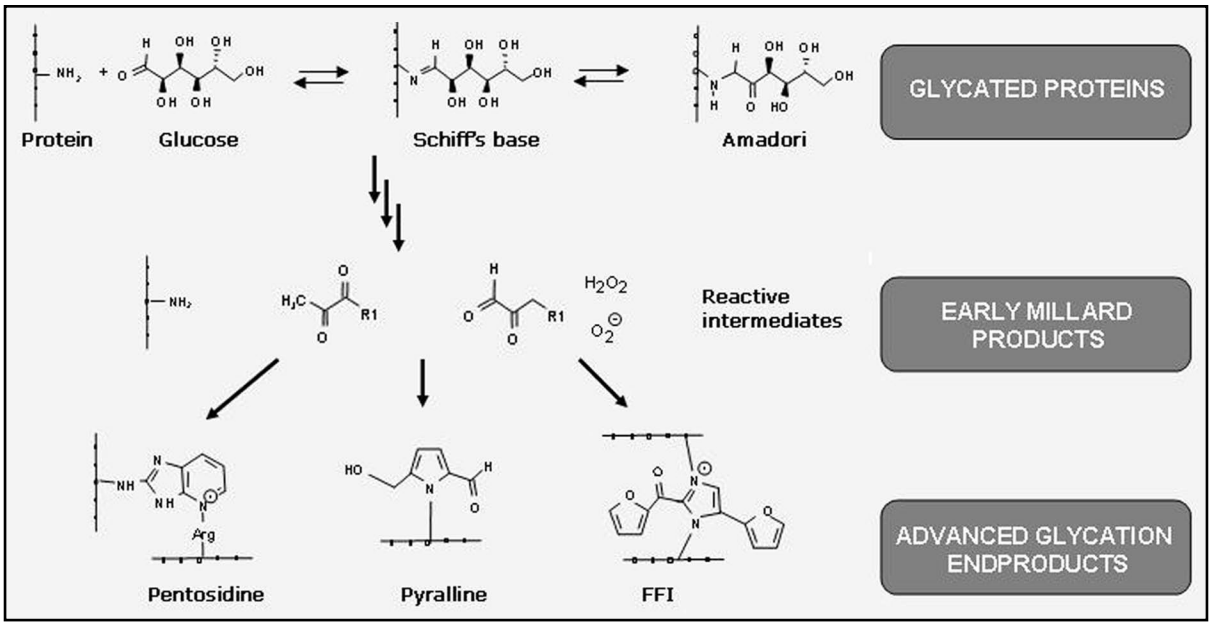

Figure 2. Chemical reactions leading to the formation of advanced glycation endproducts.

tive plaques and coronas of classic plaques. Immunohistochemical studies demostrate that AGEs colocalize to a very high degree with ApoE.[61] Accumulation of extracellular AGEs in AD is caused by an accelerated oxidation of glycated proteins ("glycoxidation").[62] Intracellular proteins deposits including NFTs, Lewy bodies of patients with Parkinson's disease and Hirano bodies are also cross-linked by AGEs,[63] which may explain their insolubility in detergents and resistance to proteases. The major component of the NFTs, the microtubuli-associated protein tau (MAP-tau) has been shown to be subject to intracellular AGEs formation. MAP-tau can be glycated in vitro, inhibiting its ability to bind to microtubules. In addition, MAP-tau isolated from brains of AD patients is glycated in the tubulin-binding region, giving rise to the formation of β-sheet fibrils.[64,65] Some studies have shown the presence of AGEs in association with two major proteins of AD, Aβ[66] and MAP-tau.[13,67] This observation supports the argument that AGEs are involved in the pathogenesis of AD.[68,69] Free radicals are involved in glycation processes and clearly can foster the formation of Aβ cross-linking.[70]

Glucose Metabolism in Alzheimer Disease

In vivo imaging of AD patients using positron emision tomography with 2-[F-18]-fluoro-2-deoxy-D-glucose demonstrates progressive reduction in brain glucose metabolism and blood flow in severe dementia. Glucose metabolism in the brain limits the synthesis of acetylcholine, glutamate, aspartate, γ-aminobutyric acid, glycine and ATP production. Whereas the cerebral energy pool is only slightly diminished during the normal aging process, glucose metabolism and cellular energy production are severely reduced in AD.[71,72] The hypothesis that genetic or environmental factors lead to an intracellular glucose hypometabolism which might predispose for both AD and adult-onset diabetes (NIDDM) is supported by large epidemologic studies. These studies demonstrate that NIDDM significantly increases the risk to develop AD.[73-77]

The first type of evidence for a link between oxidative stress (e.g., caused by Aβ) and impaired glucose transport has been shown in cultured neurons. Aβ impairs glucose transport, which is followed by a decrease in cellular ATP levels. It has been suggested that this effect is caused by conjugation of HNE, produced by lipid peroxidation, to the neuronal glucose transport protein GLUT3.[78,79] Lipid peroxidation caused by other sources of oxidative stress, such as activated microglia or free extracellular iron, may contribute to decreased glucose uptake and neuronal degeneration. This is consistent with histopathological findings in AD, where decreased membrane fluidity in mitochondria and increase levels of oxidized 8OHdG in mitochondrial DNA can be observed, and suggest a link between oxidative stress and glucose utilization.[19]

Oxidative stress and energy depletion simulated by addition of chemical uncoupling agents to neuroblastoma cells leads to the appearance of NFTs; feeding a thiamine-deficient diet to rodents leads to the formation of dystrophic neurites similar to those in AD. The oxidatively-compromised animals develop AD-type neuritic dystrophy suggesting that disturbed energy metabolism and subsequent oxidative stress may be a common denominator of neuritic dystrophy.[80]

NFTs, which are largely composed of MAP-tau protein, and senile plaques, which contain aggregates of the Aβ, are realted to disturbances in the balance between protein phosphorylation and dephosphorylation. Various studies have shown that injection of the phosphatase inhibitor okadaic acid in rat brain, results in severe memory impairment, as well as the presence of MAP-tau protein in paired helical filaments and formation of plaques containing Aβ.[81-83]

Positive Feedback Loops in the Pathogenesis of Alzheimer Disease

One of the characteristics of degenerative processes is the creation of positive feedback loops or vicious cycles. To define a vicious circle of neurodegeneration in AD, characteristic factors have to be defined which promotes the generation of ROS, amplified production of AGEs and inflammation. The "error catastrophe theory" proposes

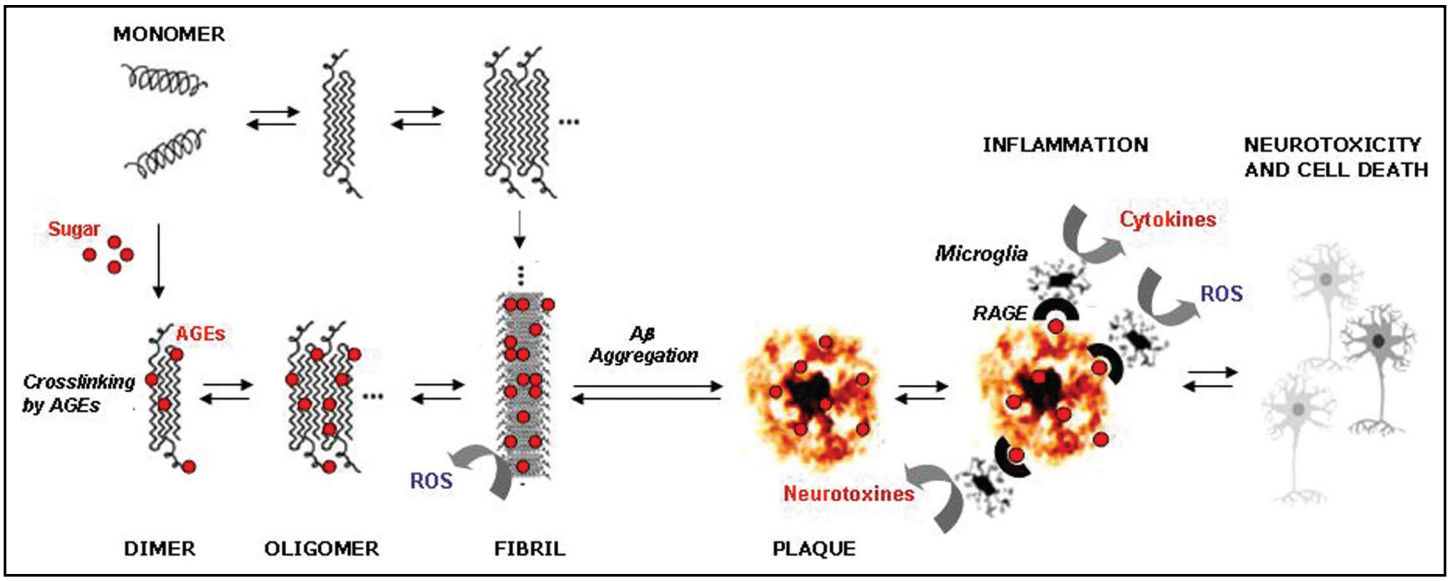

Figure 3. Direct and indirect effects of advanced glycation endproducts through crosslinking of Aβ peptide.

that damages to cell constituents accumulate during aging. At the same time, cellular defence mechanisms weaken, thus the accumulated damages cannot be repaired efficiently, leading to loss of function and finally cell death.

We propose that AGEs are one of these factors, which participate dynamicly in neuronal death and exert multiple detrimental effects on cells.[84,85] Elucidation of the effects of AGEs on cells, particularly their interaction with cell surface receptors (RAGE) and downstream signal transduction, might help to solve certain aspects of the etiopathogenesis of AD. For example, glycation and AGEs cause (Fig. 3):

• Direct radical production (chemical): Glycated proteins produce nearly 50 fold more radicals than non-glycated proteins. This process commences with the production of superoxide radicals by the transition metal-catalyzed oxidation of protein-bound Amadori products, followed by the dismutation of superoxide to hydrogen peroxide, and the generation of hydroxyl radicals by the Fenton reaction.

• Indirect radical production (cellular): Interaction of AGEs with cells increases oxidative stress. It is not clear whether this is initiated by binding of AGEs to the cell surface and subsequent diffusion of chemically produced free radicals across the membrane or by receptor mediated signalling pathway, in which a radical producing enzyme (e.g., NADPH-oxidase) and AGEs specific receptor (RAGE), is involved. Yan et al.[86] showed that RAGE is also a receptor for Aβ. This discovery supports the idea of a relation between AGEs and AD as well as the production of free radicals. The combination of AGEs and RAGE can cause oxidative stress, as shown in the production of thiobarbituric acid-reactive substances, secretion of cytokines, TNFα, heme oxygenase-1, and the activation of nuclear transcription factor κB (NFκB). Aβ binding with RAGE also elicits the macrophage colony stimulation factor which introduces an inflammatory pathway, according to a procedure linking oxidative processes and inflammation in AD.[87]

Pharmacological Interference with Age Formation or Signalling as a Novel Treatment Strategy

The development of drugs for the treatment of AD remains at a very unsatisfying state. However, pharmacological approaches which break the vicious cycle of oxidative stress and neurodegeneration offer new opportunities for the treatment of AD. These approaches include AGE-inhibitors (aminoguanidine, pyridoxamine), antioxidants (thioctic acid, vitamin E, vitamin C, β-carotin) and nonsteroidal antiinflammatory substances, which do not only scavenge radicals passively but interfere with signal transduction pathways, thereby preventing radical production.

AGE inhibitors might be able to stop formation of AGE-modified Aβ deposits or modify their structure with subsequent loss of AGEs binding to RAGE.[88,89] Antioxidants are likely to scavenge intracellular and extracellular superoxide radicals and hydrogen peroxide before these radicals damage cell constituents or activate microglia through their action as intracellular second messengers.[90-94] Antiinflammatory drugs act similarly, attenuating microglial radical and cytokine production.[95-97]

With our growing understanding of the molecular basis of the clinical symptoms of dementia, particularly positive feedback loops involving oxidative stress, it is hoped that elucidation of the etiopathogenesis of AD will help to develop novel "neuroprotective" treatment strategies able to interrupt the vicious cycle of oxidative stress and neurodegeneration.

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